II

THE TREATMENT OF GENERAL PARALYSIS OF THE INSANE BY PYROTHERAPY *

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PYROTHERAPY in its various forms has been before the notice of the medical profession for many years past. The history of pyrotherapy in general paralysis is well summarised by Petersen in his book "Protein Therapy and Non-Specific Resistance," and dates from the efforts of Jacobi in 1854, leading up to the work of V. Jauregg in Vienna on malarial therapy.

In November, 1925, the possibility of simulating malarial pyrexia by means of foreign protein suggested itself to me. Various proteins had been used in the past as fever-producing agents, and the final choice fell on T.A.B. vaccine injected intravenously for reasons which follow :

Investigation of general paralytics has shown that many of them are the subjects of chronic septic processes in addition to syphilis, and that these infective processes may be responsible for at least some of the more acute symptoms, such as restless motor excitement with destructiveness. The bacteriology of these infections has been shown to be varied and inconstant, especially such as are situate in the domain of the ear, nose and throat surgeon, and which are often the residua of that heterogeneous collection of infections which produce influenza in its many and varied forms.

According to Menninger a considerable number of instances of neurosyphilis appearing after influenza occurred at the Boston Psychopathic Hospital. The latent, incipient, and early cases of neurosyphilis seemed to be aggravated by the neurotoxic effects of influenza, but the advanced cases were not usually perceptibly altered in symptomatology or course.[1]

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Glaessner found that cases of enteric fever, both during the febrile stage and in convalescence, showed a striking immunity to influenza.[2] Theoretically, then, the production of anti-bodies of the typhoid group appeared likely, by means of some non-specific effect, to counteract the toxins of the varied groups of organisms causing influenza, which organisms had been shown to be responsible for chronic septic processes in general paralytics and were playing some part in the production of acute symptoms.

This seemed a strong argument in favour of the choice of T.A.B. vaccine as a fever-producing agent.

In addition to what we wished, namely, high and regular fever, we had an agent which would probably act beneficially by means of anti-body production.

Before the commencement of pyrexial treatment careful search should be made for hidden foci of sepsis. These may be often discovered in the accessory nasal sinuses and in the teeth sockets. Surgical treatment is indicated before proceeding further, as otherwise the vaccine often produces acute excitement as a result of intense focal reaction with pus formation in a closed space.

Material and Dosage

The material chosen was standard Burroughs Wellcome's T.A.B. vaccine, containing 1,000 million *B. Typhosus* and 750 million of *B. Paratyphosus* A and *B. Paratyphosus* B to 1 c.c.

The injections were given intravenously for ten days, starting with a dose of 300 millions total organisms and rising gradually to 6,000 millions. After a lapse of about six weeks a second course of ten injections was given, starting with a dose of 1,500 millions and rising to 20,000 millions. In the interval four injections of 0·45 gm. N.A.B. were administered. About six weeks later, after a further four injections of 0·45 gm. N.A.B., a third course of T.A.B., exactly the same as the second course, was administered in some cases.

Reactions Obtained

Usually in about half an hour after each injection of vaccine a severe rigor commences, the maximum temperature being reached in about two hours. Vomiting

and diarrhœa occur, usually most marked during the first three or four injections of each course. Herpes, usually of the ordinary febrile type, but occasionally neural in distribution, makes its appearance about the fifth day in more than half the cases. In the majority the temperature falls to normal again within twelve hours of the injection. Delay in the fall is usually due to reaction and pus formation in a closed focus of infection which has been missed in examination.

Such should be carefully searched for, special attention being paid to the X-ray search for buried dental stumps. One such delayed fall with accompanying wild excitement in a patient was traced to an abscess round a hitherto unsuspected buried root.

Temperatures up to 107° F. have been obtained, but a usual average is about 103° F.

The temperature chart of each course differs from a quotidian malarial chart only in the fact that the rise and fall is even more regular than in malaria.

Mental and Physical Changes

(1) *Mental.*—The best results are obtained in grandiose and restless cases. This is interesting in view of Smyth's observation that malaria and tryparsamide treatment produces best results in grandiose cases and in those of the agitated melancholiac type.[3] Excitement is naturally absent during pyrexia, but in nearly all cases there is no return after pyrogenic treatment has ceased. Delusions of grandeur, formerly freely expressed, become less apparent, and finally, in the majority, cannot be elicited. Misdirected motor activity leading to impulsive acts and much damage to person and property is replaced in the majority by a certain capacity to do useful ward work under slight supervision, and, in a few cases, lost initiative returns and the patient becomes a useful member of the ward community. In no case have I observed a return to complete normality. There is always, in my experience, a degree of mental enfeeblement, varying with the stage at which treatment is commenced. Naturally, other things being equal, the earlier cases are less obviously enfeebled when remission occurs than the advanced.

(2) *Physical.*—As might be expected, weight is lost during each course of injections. This loss is more than

regained in the intervals, and after active treatment has ceased the weight remains more or less steady, at a figure well above that present on admission. Muscle tone is improved, the skin is healthier in appearance, and the patient becomes more active. Some patients, admitted bedridden through gross weakness of the legs, have in the course of time been able to be up and about and do fairly useful work. I have not observed any definite alteration in established neurological signs, such as the Argyll-Robertson phenomenon or altered tendon reflexes. The power of co-ordination of the legs, arms, and muscles of articulation improves usually, but the tremor of the lower face is, as a rule, unaffected.

Serological Changes

Before the commencement of treatment the blood and C.S.F. of each case is thoroughly investigated from the serological view-point.

The blood is examined for the reactions of Wassermann and of Widal. The C.S.F. is examined for the Wassermann, Colloidal Gold, Globulin and Cell-count.

In addition, the ratio of bromine in the blood to that in the C.S.F., after the administration of bromide by the mouth, is estimated. The intensity of the Wassermann reaction is gauged by the amount of complement fixed by the specimen either of blood or of C.S.F., and that of the Widal reaction is estimated in Oxford units, so that alterations in the intensity of these reactions during treatment can be accurately observed.

No really constant change has been observed in any of the tests mentioned, and there does not appear to be any direct connection between serological change and change in the mental and physical condition of the patient. In some cases the Wassermann test, previously strongly positive in the blood and C.S.F., has become almost or quite negative in one or both, yet the patient has not done well. In others positive tests have persisted throughout treatment though the patient's mental and physical condition has improved markedly.

Bunker states that the time has not yet come to give definite prognostic views from the behaviour of the C.S.F. after malaria, and the above findings would appear to indicate that the same holds good for T.A.B. pyro-therapy.[4]

The behaviour of the Widal reaction shows marked variability in agglutinin formation in different patients, though the amount of vaccine injected was the same in each case. Typically agglutination of *B. Typhosus* and *Paratyphosus* A and B occurs in high dilution, as would be expected. A few fail to react to one or other of these organisms, some show unexpected agglutination of organisms of the same group, such as Gaertner's or Aertrycke's Bacillus, and a few show scarcely any evidence serologically of anti-body formation.

This variability of agglutinin formation in other groups of mental hospital patients has been pointed out by Pickworth, and a possible relation to focal sepsis suggested.[5]

There does not appear to be any connection between variations in the intensity of the Widal reaction and alteration of the Wassermann reaction, either in blood or C.S.F. Neither is there any apparent relation between the degree of anti-body production to the typhoid groups of organisms and prognosis as indicated by physical and mental change.

General Conclusions

It would appear that in the induction of fever at regular intervals by the intravenous injections of T.V.B. vaccine we have a means of producing remission in the course of general paralysis. In my series of thirty cases, representing all the cases admitted to the male division at this hospital, not specially chosen subjects, all but two showed remissions varying from four months to two and half years. It is scarcely likely that the small quantities of N.A.B. injected would produce this result through its anti-syphilitic action, so we are probably justified in concluding that the vaccine was the effective agent. Its effect may have been produced either through pyrexia *per se* or by reason of some obscure anti-body effect, ameliorating or eliminating the results of infection in hidden foci of sepsis or by a combination of both.

My own theory is that in general paralysis we have as a basis a diffuse syphilitic encephalitis, the tendency of which is to produce an increasing dementia capable of temporary arrest, but, in the present state of our knowledge, not of permanent arrest. Superimposed on that basis we probably have obscure toxic factors at work, pro-

ducing the more acute manifestations such as restlessness and impulsiveness, either through their direct action or indirectly through their effect in accelerating the progressive syphilitic encephalitis. It would seem that T.A.B. vaccine offers a hopeful method of attacking the latter factor.

The question of the position of leucocytosis resulting from vaccine injection and its curative effects might be raised, but from my own observations I have found no leucocytosis as a result of T.A.B. vaccine injections in these cases at any stage of the treatment. This observation I know differs from that of other workers, but it is significant in view of the fact that leucopenia occurs in typhoid fever.

Some of the advantages of T.A.B. as a means of producing regular fever, apart from any anti-body effect, may be submitted.

(1) The material injected is standardised, and the dose can be regulated with exactitude.

(2) The method of administration is simple and free from risk of accident if ordinary care is exercised.

(3) The injections can be stopped at once in the event of any untoward symptoms arising. This has on no occasion been necessary in my experience.

(4) The treatment incidentally confers a high degree of immunity to the typhoid group of infections, provided a reasonable interval of about six weeks is allowed to elapse between each course of fever-therapy in order to minimise the possibility of exhaustion of the anti-body producing mechanisms. This is a valuable factor to be borne in mind from the point of view of the general health of mental hospitals.

(5) In no case has death been found to have been precipitated or accelerated by the injections.

End Results of Treatment

It is not claimed or even suggested that we have at last found a cure for general paralysis in this particular form of pyrotherapy. These cases continue to die of general paralysis and to show post-mortem changes typical of the condition. What is suggested is that T.A.B. pyrexia induces remission in a very large proportion of cases, is easily carried out and free from

danger, and is at least worth an extensive trial over a prolonged period until such time as a more powerful therapeutic agent is discovered.

Life is certainly prolonged, and during the remission the patients are quiet and amenable ; many are interested in their surroundings and able to do fairly useful ward work. They can be brought from states of excitement, exaltation, impulsiveness and destructiveness to a condition of remission with mental enfeeblement varying in degree with the stage at which treatment is commenced and requiring the minimum of nursing attention until such time as relapse occurs and gradually increasing weakness leads to the end.

On numerous occasions I have pondered over the question of discharge during the remission. The cases I have treated have belonged exclusively to the lower and working classes, and the conditions of home life, including financial resources with attendant possibility of reasonably frequent attention to matters of general health, have warranted the continued institutional care and treatment of a number who would probably have been discharged had they been situated in a higher walk of life or had been under treatment earlier.

References

(1) Menninger. *Arch. Int. Med.*, 1919, Vol. 24, pp. 98–115.
(2) Glaessner. " Beobachtungen bei der Grippepneumonie," *Wein. Klin. Wchnschr.*, 1919, Vol. 32, pp. 200–201.
(3) Smyth. *Jl. Ment. Sc.*, Oct., 1928, pp. 687–708.
(4) Bunker. *Arch. of Neur. and Psychiat.*, March, 1928.
(5) Pickworth. *Jl. Ment. Sc.*, Oct., 1928, pp. 709–719.